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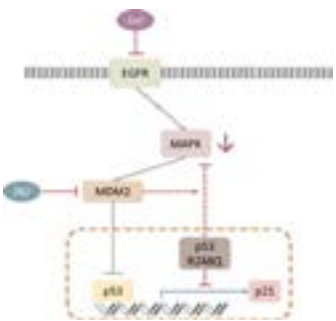
p53 R248Q mutation alters molecular trafficking and targeted drug responses in ovarian cancer

Kai-Yun Tsai
National Tsing Hua University, Taiwan

The dysfunction of tumor suppressor p53 and its regulators is a common feature of human cancer, including ovarian cancer. Specifically, the genetic alteration of p53 mutation is detected in up to 96% of high-grade serous ovarian carcinoma (HGSOC). Moreover, mutant p53 may cause oncogenic gain-of-function phenotypes under sustained activation of EGFR signaling. Thus, we aimed to investigate whether p53 mutation could affect combined inhibition of EGFR and the p53-specific ubiquitin ligase MDM2 in ovarian cancer. We selected p53 R248Q mutant, which has the highest mutation frequency in cancer, for this study. We found that, when p53 R248Q was transiently overexpressed, the p-AKT protein expression would increase significantly. Immunocytochemistry analysis further showed that, upon EGF stimulation or p53 R248Q mutant overexpression, several EGFR pathway and cross-talking mediators would translocate in unique patterns within the cell. Previously, we have demonstrated that combined inhibition of EGFR and MDM2 pathways by Gefitinib and JNJ exerts strong synergistic inhibition on p53-mutated HGSOC cells. Our immunofluorescence analysis revealed that, under such combined inhibition, the cytonuclear trafficking of these mediators would be disrupted. Moreover, when we compared the drug responses in different p53 status, we observed the sensitivity to single- or combined-inhibition treatments would be altered in p53 R248Q overexpressed cells. In summary, our findings suggest that p53 R248Q mutation might cause differential responses in signal transduction, molecular trafficking, and drug efficacy, which helps to advance our understanding in p53 signaling and cancer biology and to improve future therapeutic strategies on HGSOC.



Biography

Kai-Yun Tsai is pursuing her Master's degree. She has experience with two research labs in applying professional knowledge to study unresolved medical challenges. Her recent work sheds light on the importance of p53 R248Q mutation in HGSOC with different drug responses. She was selected to be a valedictorian of National Tsing Hua University.

a0956568498@gmail.com

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